THE REMARKS

The Amendments

Claims 3-15 and 22-25 are pending.

The amendments in the specification at page 19 and in Claim 12 are to correct grammatical errors.

Claim 22 is amended to delete 2' or 3' phenylcarbamate UTP; 2',3' di-phenylcarbamate UTP; and 2',3' phenylacetaldehyde acetal ADP.

Claim 23 is amended to delete 2-(3-trifluoromethylpropyl)thio-6-(2-methylthio) ethylamino-2',3'-(benzyl)methylenedioxy purine riboside 5'-α, β-difluoromethylene dipohsphate.

No new matter is added in any of the above amendments. The Examiner is requested to enter the amendment and reconsider the application.

35 U.S.C. §112, Second Paragraph Rejection

Claims 22-23 are rejected under 35 U.S.C. §112, second paragraph because some compounds do not read upon a dinucleotide. Applicants have amended Claims 22 and 23 such that all compounds in Claims 22 and 23 now read upon a dinucleotide.

Therefore, the §112, second paragraph rejection of Claims 22 and 23 should be withdrawn.

35 U.S.C. §103(a) Rejections

Claims 3-15 and 22-25 are rejected under 35 U.S.C. §103(a) as being unpatentable over combination of Zamecnik, U.S. Patent No. 5,049,550 (Zamecnik); Yerxa, *et al.*, U.S. Patent No. 6,323,187; Kim, *et al.*, *Journal of Biological Chemistry* (1994), Vol. 269, pages 6471-6477; and Markland, *et al.*, U.S. Patent No. 5,814,609. The rejection is traversed.

The present invention is directed to a method of preventing or treating diseases or conditions associated with platelet aggregation by administering to a subject a pharmaceutical composition comprising a therapeutic effective amount of $P2Y_{12}$ receptor **antagonist** compound, which is a dinucleotide compound of Formula I, wherein at least one of the Y' and Z' positions is OR_1 or OR_2. The present invention teaches dinucleotide derivatives having at least one modified

hydroxyl at 2' or 3' on the sugar moiety for use as inhibitors of $P2Y_{12}$ activation by ADP, thereby inhibiting platelet aggregation.

1. Zamecnik

Zamecnik discloses the use of diadenosine 5',5'''-p^1,p^4-tetraphosphate (AP_4A), or an analogue thereof, as an antithrombotic agent (column 3, lines 4-59). The analogues that Zamecnik refers to only have the modification on the tetraphosphate chain such as CHF, CHCl, and CHBr. Zamecnik does not teach or suggest modification on the ribose moiety. As the Examiner admits, Zamecnik differs from the instantly claimed invention in that (a) Zamecnik does not teach analogs wherein at least one of the 2'- or 3'-positions is OR_1 or OR_2, and (b) Zamecnik does not teach the dinucleotides as $P2Y_{12}$ receptor antagonists.

2. Yerxa, *et al.*

Yerxa, *et al.* disclose P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphate and its salts, esters, and amides thereof, which are **agonists** of $P2Y_2$ and/or $P2Y_4$ purinergic receptors. Yerxa, *et al.* also disclose methods of enhancing secretion clearance and enhancing ciliary beat frequency in a mammal using P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphate. Yerxa, *et al.* do not disclose the instant compounds or the instant use.

(a) $P2Y_{12}$ antagonists vs. $P2Y_2$ and/or $P2Y_4$ agonists

Yerxa, *et al.* disclose compounds that are **agonists** of the $P2Y_2$ and/or $P2Y_4$ purinergic receptor. The instant application teaches a $P2Y_{12}$ receptor **antagonist**. An antagonist is an agent that binds to a receptor and reduces the action of another agent, the agonist. An antagonist works in opposition to the agonist. Further, $P2Y_{12}$ receptor is different from $P2Y_2$ or $P2Y_4$ purinergic receptor.

The compounds used in the present methods are functionally different from those disclosed in Yerxa, *et al.* in that the present compounds are **antagonists** of $P2Y_{12}$ receptors, whereas the Yerxa compounds are **agonists** of $P2Y_2$ and/or $P2Y_4$ purinergic receptors. Yerxa, *et al.* do not teach or suggest the instant receptor or an antagonist.

(b) Difference in Chemical Structures

The dinucleotide compounds used in the present methods are structurally different from those disclosed in Yerxa, *et al.* in that:

Y'= H, OH, or OR_1,

Z'= H, OH or OR_2,

with the proviso that at least one of Y', and Z', is OR_1 or OR_2, (instant Claim 3)

With the above proviso, one of Y' and Z'is an ether, ester, thioester, carbamate, thiocarbamate, cyclical acetal, cyclical ketal, or cyclical orthoester.

Yerxa, *et al.* disclose P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphates (where Y, Y', Z and Z' all equal to OH) and its salts, esters, and amides thereof. However, Yerxa, *et al.* do not teach or suggest that Y' or Z' is an ester. Applicants were the first that discovered the modification of Y' and Z' on dinucleotides and the use of such compounds in preventing or treating platelet aggregation. Applicants have made such compounds and demonstrated its use. Without the teaching of instant application, a skilled person in the art would not have modified P^1-(cytidine 5')-P^4-(uridine 5'-)tetraphosphates on the Y' or Z' position because the outcome is unpredictable and there is no motivation to do so.

(c) Difference in Diseases Treated.

Yerxa, *et al.* disclose methods of enhancing secretion clearance and enhancing ciliary beat frequency in a mammal. Yerxa, *et al.* also disclose methods of treating sinusitis, otitis media, dry eye disease, and retinal detachment. Yerxa, *et al.* do not teach or suggest a method of preventing or treating diseases or conditions associated with platelet aggregation.

3. Kim, *et al.*

(a) Kim, *et al.* do not disclose dinucleotide compounds.

Kim, *et al.* disclose some mononucleotide compounds such as adenosine 5'-O-(1-thiotriphosphate), ATP, adenosine 5'-O-(3-thiotriphosphate), 3'-O-(4-benzoyl-benzoyl)ATP, α,β- and β,γ-methylene ATP. Kim, *et al.* do not teach or suggest any dinucleotide compound.

(b) Kim, *et al.* do not teach or suggest using $P2Y_{12}$ receptor antagonist to treat platelet

aggregation.

The purpose of Kim, *et al.* is to describe "a purinergic P2 receptor on PC12 cells that does not fit the classification for the P_2x, P_2y, P_2t, P_2u, P_2z receptor subtypes." (See Abstract last sentence)

Platelet aggregation is only mentioned in the reference at page 6471, first paragraph under the Abstract:

> Extracellular nucleotides can influence many biological functions, including platelet aggregation, vascular tone, cell division, cardiac and skeletal muscle contraction, as well as peripheral and central neurotransmission (1). These extracellular actions of ATP are mediated through purinergic receptors that have been classified by Burnstock (2) as P2 receptors."

The above paragraph only discloses that ATP (an extracellular mononucleotide) can influence platelet aggregation. Kim, *et al.* do not teach that agonists of P2Y purinergic receptors inhibit or modulate platelet aggregation as the Examiner asserted in the Office Action (Page 6). In any case, agonists of P2Y purinergic receptors are irrelevant to the instant invention, which teaches antagonists of $P2Y_{12}$ purinergic receptors.

4. U.S. Patent 5,814,609 (Markland, *et al.*)

Markland, *et al.* discloses that peptides such as contortrostatin found in snake venom can inhibit ADP-induced platelet aggregation. Markland, *et al.* do not disclose purinergic receptors or dinucleotide compounds. The mechanism of action suggested in Markland does not relate to $P2Y_{12}$ receptors; Markland suggests that it relates to binding of the material to GPIIb/IIIa integrin receptors.

5. Combination of References

None of the above-cited references have taught or suggested antagonists of $P2Y_{12}$ purinergic receptors. None of the above-cited references have taught or suggested a dinucleotide compound of Formula I, wherein at least one of the Y' and Z' positions is OR_1 or OR_2. Applicants were the first to make such compounds and to suggest the use of such compounds in preventing or treating platelet aggregation.

Applicants respectfully disagree with the Examiner's assertion that one of ordinary skill would have been motivated to modify 2'-or 3'-position to the corresponding ester or amide based on the teachings of Yerxa and Kim (Office Action page 6). Kim does not teach dinucleotides. Yerxa does not teach platelet aggregation. There is no motivation to combine the two applications. Even assuming there is motivation, Yerxa does not teach or suggest the modification on the ribose moiety, therefore, the combination of the two references does not produced the instant compounds. Without the teaching of instant application, a skilled person in the art would not have modified dinucleotides on the Y' or Z' position because the outcome is unpredictable and there is no motivation to do so. There is simply no hint in any of the cited references regarding the modification of dinucleotides on the Y' or Z' position; there is also no hint that such modification would produce compounds useful for preventing or treating platelet aggregration.

Even with hindsight construction following Applicants' disclosure, the combination of Zamecnik, Yerxa, *et al.,* Kim, *et al.* and Markland, *et al.* do not produce the instant Claims. Therefore, the 35 U.S.C. §103(a) rejection of Claims 3-15 and 22-25 should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned.

Respectfully submitted,

Date: July 30, 2004

Viola T. Kung (Reg. No. 41,131)

HOWREY SIMON ARNOLD & WHITE, LLP
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
Ph. (650) 463-8181